FREEDOM OF INFORMATION SUMMARY

Public Master File 5673

Tilmicosin Phosphate

"...for the treatment of bacterial pneumonia due to *Pasteurella* (*Mannheimia*) *haemolytica* in sheep."

Sponsored by:

NRSP-7

PMF 5673

FOIS 1

I. GENERAL INFORMATION

PMF Number:	5673
Sponsor:	NRSP-7 Southern Region College of Veterinary Medicine University of Florida Gainesville, Florida 32610
Accepted Name:	Tilmicosin phosphate
Supplemental Effects:	The approval of a supplement to an already approved product will allow for the use of tilmicosin injection for the treatment of bacterial pneumonia due to *Pasteurella* (*Mannheimia*) *haemolytica* in sheep.
Minor Species Classification	Sheep are classified as a minor species. Therefore, this Public Master File addresses minor species requirements with respect to effectiveness and target animal safety data collection.

II. INDICATION FOR USE

Tilmicosin injection is indicated for the treatment of bacterial pneumonia due to *Pasteurella* (*Mannheimia*) *haemolytica* in sheep.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. *Dosage Form*: Tilmicosin Injection (300 mg/mL).

B. *Route of Administration*: Subcutaneous injection between scapulae

C. *Recommended Dosage*: Administer Tilmicosin injection to sheep at the dosage of 10 mg per kg body weight

D. *Recommended Dosage Rate*: Once

IV. EFFECTIVENESS

Section 514.1(d) of Title 21 of the Code of Federal Regulations (CFR) permits extrapolation of data from a major species to a minor species to satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act with respect to the effectiveness of a new animal drug. A combination of data from sheep (a minor species) and a closely-related approved major species (cattle) were used to support the determination of effectiveness, consistent with the *Guidelines for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor Use of Animal Drugs* (FDA/CVM April 1986).

A summary of a study demonstrating the comparative pharmacokinetics of tilmicosin injection in cattle and sheep is provided.

A. Type of Study: Pharmacokinetic and Pharmacodynamic Properties of Tilmicosin in Sheep and Cattle

B. Name and Address of Investigators:

Drs. Sanja Modric and Alistair Webb
Department of Physiological Sciences
College of Veterinary Medicine
University of Florida, P.O. Box 100144
Gainesville, Florida 32610

C. General Design of the Investigation:

1) Purpose of the study: To compare the serum concentrations of tilmicosin in serum of sheep and cattle following a single subcutaneous injection of tilmicosin at a dose of 10 mg/kg body weight.

2) Test animals: Ten cross-bred non-pregnant adult female sheep were allocated for this study. The animals had been acclimated at the University of Florida for six months prior to the initiation of the study. The animals ranged in age from 2 to 6 years. The body weights ranged from 120 to 170 pounds.

Ten young Angus cows, recently weaned of their calves were allocated for this study. The animals were acclimated for two months prior to the start of the study. The cows ranged in age from 2 to 3 years. The body weights ranged from 865 to 1065 pounds. All cattle and sheep were identified by ear tags.

3) Treatment Groups: The sheep experiment was a cross-over design with animals randomly assigned to treatment and placebo (saline) groups. Following a two-week washout period, the groups were reversed. Tilmicosin was administered subcutaneously between the scapulae at a dose of 10 mg/kg body weight for the treatment group. For the placebo group, an equivalent volume of saline was injected.

All of the cattle received a single subcutaneous injection of tilmicosin at a dose of 10 mg/kg body weight.

4) Sampling: Serum samples were collected from each animal according to the following schedule: 0 min, 5 min, 15 min, 30 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 30 hr, 36 hr, 48 hr, 60 hr, 72 hr, and 96 hr.

5) Dosage Form: Tilmicosin Injection (300 mg/mL).

6) Route of Administration: Subcutaneous injection.

7) Dosages used: 10 mg/kg of body weight.

8) Test Duration: approximately 22 days

9) Parameters: Serum drug concentrations at each of the specified timepoints, cardiopulmonary measures (ECG, heart rate, systolic, diastolic, and mean blood pressure), daily physical examination (respiratory rate, heart rate, body temperature), and evaluation of attitude, appetite, elimination, behavior, and monitoring of any adverse effects.

D. Results:

Pharmacokinetic data analysis: Serum tilmicosin concentrations were evaluated for the following pharmacokinetic measures:

$AUC_{0\text{-last}}$: area under the concentration/time profile measured from time zero to the last quantifiable concentration (last concentration at or above the limit of quantification of the analytical method). AUC estimates were based upon the trapezoidal rule.

$AUC_{0\text{-inf}}$: AUC measured from time zero to time infinity based upon the equation: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last}/\beta$; where C_{last} is the last concentration at or above the limit of quantification of the analytical method and β = the terminal slope of the lnC vs time profile.

CMAX = the observed maximum serum tilmicosin concentration

TMAX = the time to CMAX

T1/2 = $0.693/\beta$

$CL_{systemic}/F$ = $Dose/AUC_{0\text{-inf}}$

Vd_{area}/F = $Vd\beta = CL_{systemic}/\beta * F$

The 90% confidence interval about the difference between cattle and sheep serum level data (2 one-sided test procedure, expressed relative to the cattle mean values) were computed for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and CMAX.

Tilmicosin was more bioavailable in sheep as compared to cattle, as indicated by the relative values for AUC and CMAX. Due to irregularities in the terminal serum concentrations, the estimates of terminal half lives vary markedly, depending upon points selected for the terminal regression analysis. Nevertheless, the half life was consistently longer in sheep as compared to cattle, and this difference was attributable to the smaller $CL_{systemic}/F$ and larger Vd_{area}/F of sheep. Marked differences were also noted in TMAX.

Table 4.1. Summary of Pharmacokinetic Values for Tilmicosin in Sheep and Cattle

	Sheep (mean +/-SD)	cow (mean +/-SD)	sheep/cow ratio	lower CI (untransformed)	upper CI (untransformed)
$AUC_{0\text{-last}}$ (μg*hr/mL)	17.14 +/- 3.41	15.29 +/- 3.58	1.12	94	130
$AUC_{0\text{-inf}}$* (μg*hr/mL)	23.6 +/- 3.74	18.8 +/- 5.51	1.26	106	145
CMAX (μg/mL)	0.82 +/- 0.22	0.87 +/- 0.42	0.94	64	124
TMAX (hr)	3.9 +/- 2.4	0.50 +/- 0.67			
T1/2* (hr)	60 +/- 25	39 +/- 32	1.54	median sheep = 50 hours	median cow = 27 hours
Clearance (L/hr*kg/F)	0.45 +/- 0.09	0.56 +/- 0.16	0.80		
Vd_{area} (L/kg*F)	37.2 +/-13.1	26.6 +/- 10.02	1.40		

When the logarithmic concentrations of tilmicosin were plotted against time, the resulting curves for the sheep and cattle consisted of two distinct parts, indicating a two-compartment body model. The disposition profiles of tilmicosin showed differences in both rate of absorption and terminal rate of drug elimination. For sheep, tilmicosin was absorbed more slowly, but concentrations were maintained for a longer duration of time as compared to cattle. Therefore, exposure after a single dose was significantly higher in sheep as compared to cattle. Since the therapeutic effects of tilmicosin are based upon time above MIC, this difference in serum tilmicosin concentrations suggest that the drug should be of comparable efficacy in sheep and cattle. Moreover, since maximum concentrations were greater in cattle as compared to sheep, it is determined that animal safety will not be compromised by the increase in total drug exposure when tilmicosin is administered as a single dose.

Cardiovascular Effects: A two-way repeated measures ANOVA was performed to compare each cardiovascular parameter between the tilmicosin- and saline-treated sheep.

In the statistical analysis, the effect of treatment was found to be significant for the systolic and mean blood pressure, while it was not significant for the diastolic blood pressure. During both placebo control and treated conditions, blood pressure varied significantly as a function of time.

The data show that the heart rate in sheep was slightly increased in tilmicosin-treated animals, except for the first two time points. However, in the statistical analysis, there was no significant difference in heart rate between the treated and non-treated sheep. The effect of time was significant for both treatment groups. There was no significant difference in the interaction of treatment and time in the analysis of the effect of tilmicosin on the heart rate.

Statistical analysis revealed no significant effect of tilmicosin on the sheep respiratory rate. The effect of time was found to be significant in both treatment groups, so that there was a notable decrease in respiratory rate over time. There was no significant interaction between the treatment and time in the analysis of the effects of tilmicosin on the respiratory rate in sheep.

Blood Chemistry and Hematology in Sheep and Cattle: Initial blood chemistry and hematology results fell within the normal ranges for each species. Samples for CBC and chemistry analyses were collected before treatment, and at 24 and 72 hours after treatment in both sheep treatment groups.

Statistical analysis using the two-way repeated measures ANOVA revealed that there was no significant effect of treatment on any parameter of the CBC/Chemistry analysis.

E. Conclusion:

The comparative study of tilmicosin pharmacokinetics in sheep and cattle indicates that the target animal safety and product efficacy should be comparable in sheep and cattle when tilmicosin is administered as a single subcutaneous injection at a rate of 10 mg/kg.

In this study, using the labeled dose of 10 mg/kg body weight and the subcutaneous route of injection, no adverse effects of tilmicosin were found on blood pressure, heart rate, or respiratory rate of sheep.

V. TARGET ANIMAL SAFETY:

Target animal safety of tilmicosin was determined during the pharmacokinetic study described above under Effectiveness. None of the animals died during the study and no adverse effects of tilmicosin were observed on blood pressure, heart rate, or respiratory rate of sheep treated once by a subcutaneous injection of 10 mg/kg dose. The results indicate that tilmicosin can be used safely in sheep at the recommended dose.

VI. AGENCY CONCLUSIONS

The data submitted in this public master file (PMF) are supporting information for the effectiveness, target animal safety, and environmental data required by Section 512 of the Food, Drug, and Cosmetic Act with regard to the proposed use of tilmicosin phosphate injection for the treatment of sheep respiratory disease (pneumonia) associated with *Pasteurella* (*Mannheimia*) *haemolytica*. Sheep are a minor species of animals defined under 21 CFR 514.1(d)(1)(ii). The data submitted meet the requirements of that regulation, and FDA's "Guidance for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor Use of Animal Drugs" (April 1986). FDA will consider this information along with other required data as support for NADAs that may be filed for this use of tilmicosin phosphate injection in sheep.

Under FDA National Environmental Policy Act (NEPA) regulations, section 21 CFR 25.33(d)(4) provides a categorical exclusion from the requirement to prepare an Environmental Assessment (EA) for minor species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. The Agency agrees that sheep are a minor species and that the management practices for sheep are the same as for goats or cattle. An applicant may claim a categorical exclusion under 21 CFR 25.33(d)(4) provided the applicant can state that to the applicant's knowledge, as in 21 CFR 25.15, no extraordinary circumstances exist. It is assumed that the applicant has made a reasonable effort to determine that no extraordinary circumstances exist.

FDA is publishing a notice of availability of this PMF to encourage sponsors to file new animal drug applications (NADAs) for tilmicosin phosphate injection for the use covered by the PMF. Sponsors of NADA's or supplemental NADA's may, without further authorization, reference the PMF to support approval of an application filed under 21 CFR 514.1(d). An NADA or supplemental NADA must include, in addition to reference to the PMF, animal drug labeling and other information needed for approval, such as data supporting extrapolation from a major species in which the drug is currently approved or authorized reference to such data; data concerning manufacturing methods, facilities, and controls; data concerning human food safety; and information addressing potential environmental impacts of the manufacturing process.

Tilmicosin phosphate is currently approved for use in cattle (21 CFR 522.2471), as a single subcutaneous injection, at a dosage of 10 mg/kg body weight.